Genome-wide analysis of the bHLH gene family in planarians identifies factors required for adult neurogenesis and neuronal regeneration.

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Public Summary:
Neural stem cell differentiation is regulated by proneural basic helix-loop-helix (bHLH) transcription factors, which bind DNA to regulate gene expression. These genes are conserved in widely divergent animals and are known to have multiple roles in development. However, the gene targets of most bHLH genes are not known. As a first step to examine the role of bHLH genes in planarian cell fate specification, we performed a genome-wide characterization of the bHLH family in Schmidtea mediterranea. We identified 44 planarian bHLH homologs, characterized their pattern of gene expression in the animal, and examined their function in regenerating and uninjured planarians using RNAi. Based on their patterns of expression in stem cells or their progeny, neurons, and RNAi phenotypes, our analysis has uncovered nine bHLH homologs with roles in neural differentiation.

Scientific Abstract:
In contrast to most well-studied model organisms, planarians have a remarkable ability to completely regenerate a functional nervous system from a pluripotent stem cell population. Thus, planarians provide a powerful model to identify genes required for adult neurogenesis in vivo. We analyzed the basic helix-loop-helix (bHLH) family of transcription factors, many of which are crucial for nervous system development and have been implicated in human diseases. However, their potential roles in adult neurogenesis or central nervous system (CNS) function are not well understood. We identified 44 planarian bHLH homologs, determined their patterns of expression in the animal and assessed their functions using RNAi. We found nine bHLHs expressed in stem cells and neurons that are required for CNS regeneration. Our analyses revealed that homologs of coe, hes (hesl-3) and sim label progenitors in intact planarians, and following amputation we observed an enrichment of coe+ and sim+ progenitors near the wound site. RNAi knockdown of coe, hesl-3 or sim led to defects in CNS regeneration, including failure of the cephalic ganglia to properly pattern and a loss of expression of distinct neuronal subtype markers. Together, these data indicate that coe, hesl-3 and sim label neural progenitor cells, which serve to generate new neurons in uninjured or regenerating animals. Our study demonstrates that this model will be useful to investigate how stem cells interpret and respond to genetic and environmental cues in the CNS and to examine the role of bHLH transcription factors in adult tissue regeneration.